Pharmaceutical Chemistry

Antibacterial Antibiotics

Lecture 5

Sulfonamides

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College of Pharmacy

Antibacterial agents which act against cell metabolism (antimetabolites)

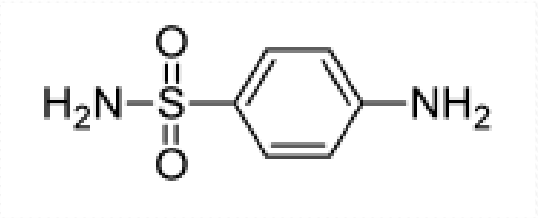
Antibacterial sulfonamides

The sulfonamide antimicrobial drugs were the first effective chemotherapeutic agents that could be used systemically for the cure of bacterial infections in humans. Their introduction led to a sharp decline in the morbidity and mortality of infectious diseases. The rapid development of widespread resistance to the sulfonamides soon after their introduction and the increasing use of the broader-spectrum penicillins in the treatment of infectious disease diminished the usefulness of sulfonamides.

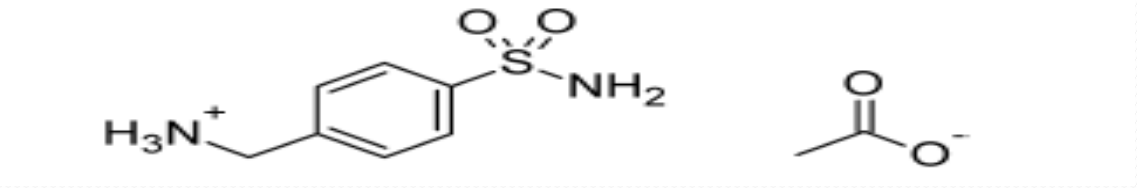
Nomenclature of the Sulfonamides

Sulfonamide is a generic term that denotes three different cases:

1. Antibacterials that are aniline-substituted sulfonamides (the "sulfanilamides").



2. Prodrugs that react to generate active sulfanilamides (i.e., sulfasalazine).
3. Non aniline sulfonamides (i.e., mafenide acetate).



Spectrum of Action of theSulfonamides

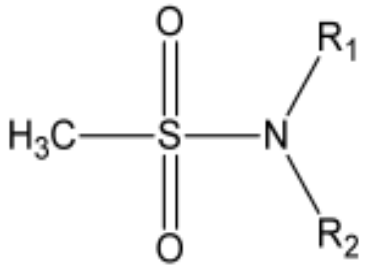
Sulfonamides inhibit Gram-positive and Gram-negative bacteria, nocardia, Chlamydia trachomatis, and some protozoa.

Some enteric bacteria, such as E. coli and Klebsiella, Salmonella, Shigella, and Enterobacter spp. are inhibited.

Sulfonamides today used as combination

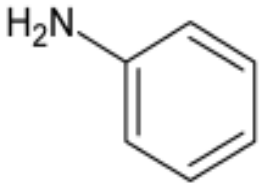
Trimethoprim (Cotrimoxazole) as antibacterial

Pyrimethamine (Cotrimazine) as anti-Malarial.

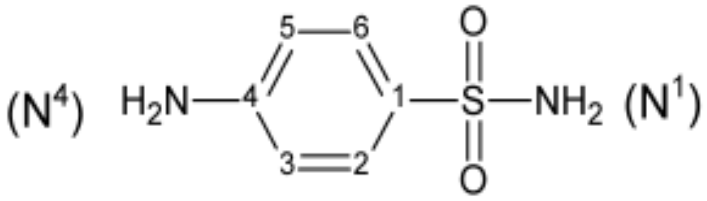


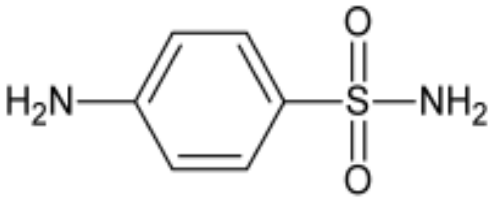
General Sulfonamide Structure

Aniline

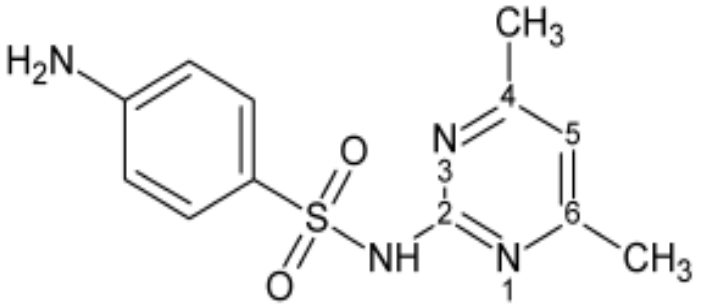


Sulfanilamide





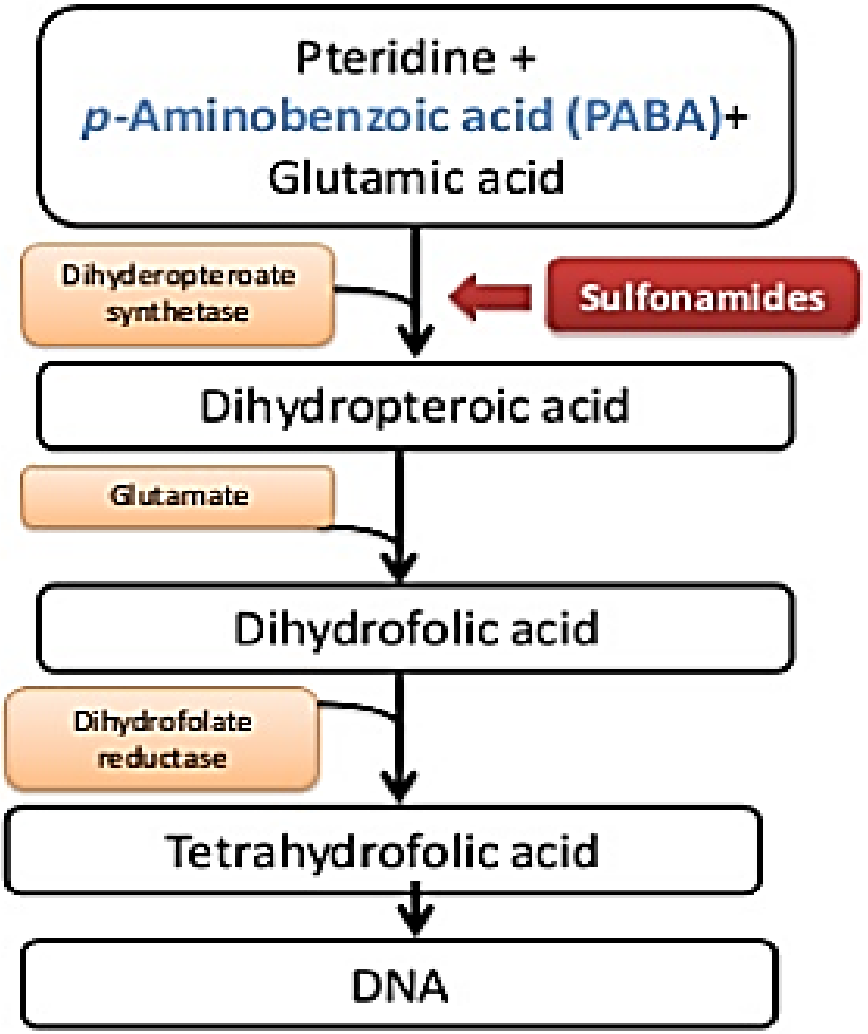
Sulfanilamido-



Sulfamethazine:
N^1-(4,6-Dimethyl-2-pyrimidyl)sulfanilamide

Mechanism of action

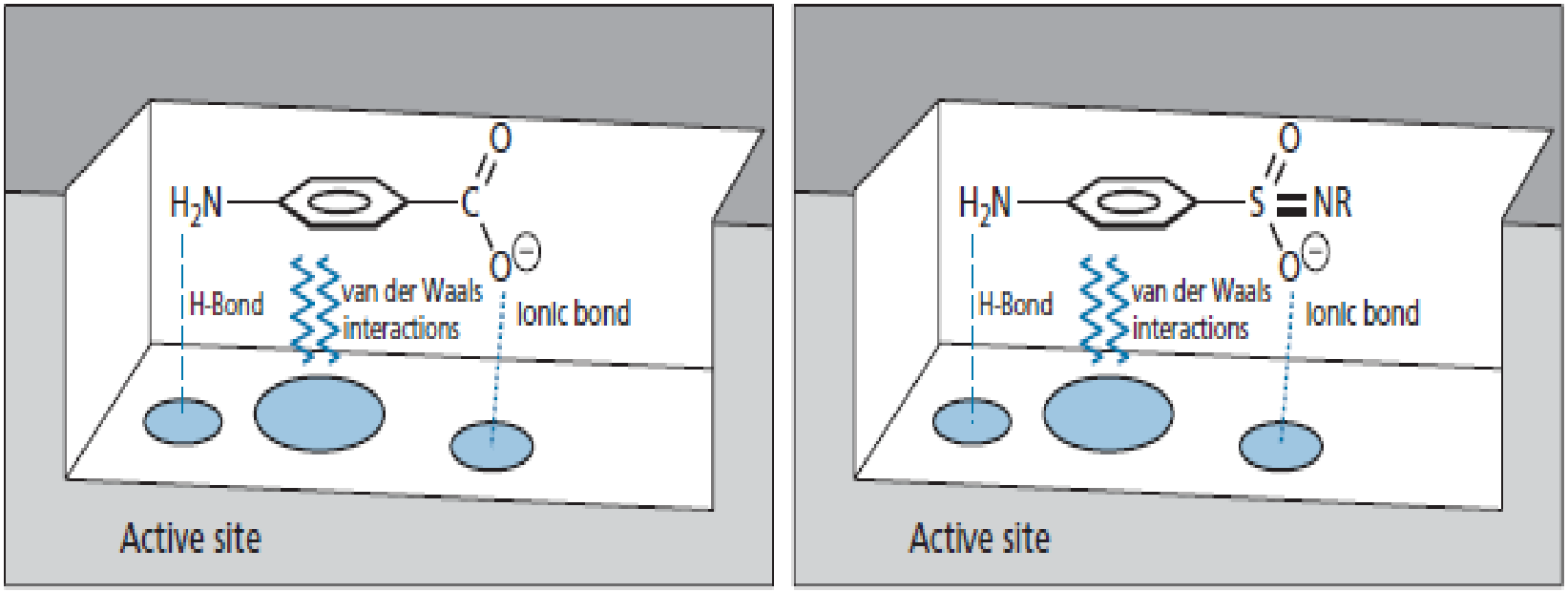
- Bacteria synthesize their own folic acid (FA) of which *p*-aminobenzoic acid (PABA) is a constituent, and is taken up from the medium.
- Sulfonamides, are structural analogues of PABA, inhibit bacterial folate synthase and formation of folate get inhibited.
- Sulfonamides competitively inhibit the PABA with pteridine residue to form dihydropteroic acid which conjugates with glutamic acid to produce dihydrofolic acid.
- Sulfonamide altered folate an which is metabolically injurious



Sulphonamides act as inhibitors by mimicking p - aminobenzoic acid (PABA)—one of the normal substrates for dihydropteroate synthetase.

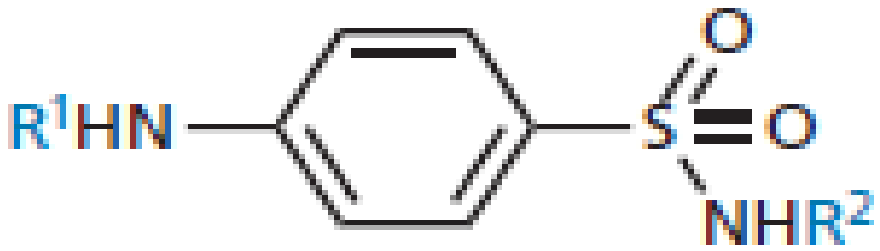
The sulphonamide molecule is similar enough in structure to PABA that the enzyme is fooled into accepting it into its active site. Once it is bound, the sulphonamide prevents PABA from binding. As a result, dihydropteroate is no longer synthesized.

Sulphonamides are competitive enzyme inhibitors so inhibition is reversible.



Sulphonamide prevents PABA from binding by mimicking PABA.

Structure–activity relationships



1. The para -amino group is essential for activity and must be unsubstituted (i.e. R 1 = H).

The only exception is when R 1 = acyl (i.e. amides).

The amides themselves are inactive but can be metabolized in the body to regenerate the active compound).

Thus, amides can be used as sulphonamide prodrugs;

2. The aromatic ring and the sulphonamide functional group are both required;

3. Both the sulphonamide and amino group must be directly attached to the aromatic ring

4. Varying R_2 can also affect the solubility of sulphonamides. Variations of R_2 affect the pharmacokinetics of the drug, rather than its mechanism of action

5. The aromatic ring must be para -substituted only.

6. Extra substitution eliminates activity for steric reasons

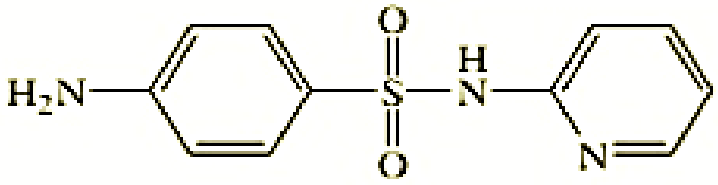
7. The sulphonamide nitrogen must be primary or secondary

8. R_2 is the only possible site that can be varied in Sulphonamides.

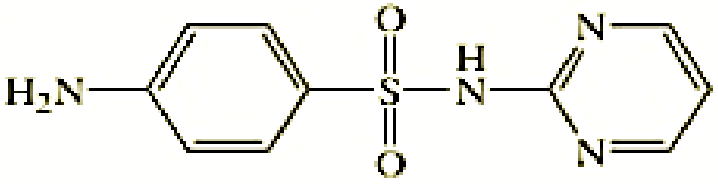
Sulphanilamide analogues

In sulphanilamide analogues, R 2 is often varied by incorporating a large range of heterocyclic or aromatic structures which affects the extent to which the drug binds to plasma protein. This, in turn, controls the blood levels and lifetime of the drug. Thus, a drug that binds strongly to plasma protein will be released slowly into the blood circulation and will be longer lasting.

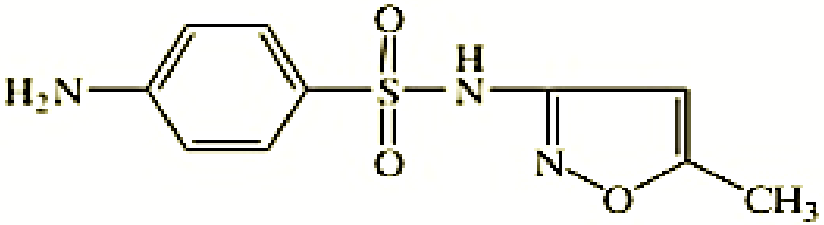
Sulfonamide Structures



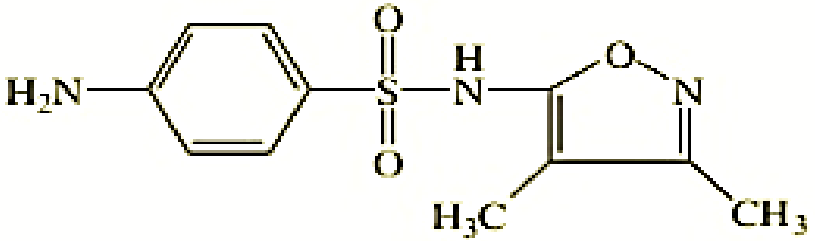
Sulphapyridine



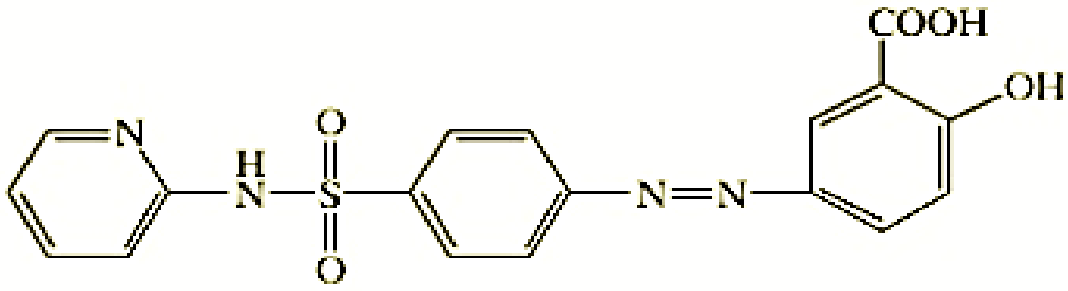
Sulfadiazine



Sulfamethoxazole



Sulfisoxazole



Sulfasalazine

Pharmacokinetics of Sulfonamides

- **Oral-absorbable**
  - **Short acting**
    - Sulfacytine
    - Sulfisoxazole
    - Sulfamethizole
  - **Intermediate acting**
    - Sulfadiazine
    - Sulfamethoxazole
    - Sulfapyridine
  - **Long acting**
    - Sulfadoxine
- **Oral-nonabsorbable**
  - Sulfasalazine
- **Topical**
  - Sodium sulfacetamide
  - Mafenide acetate
  - Silver sulfadiazine

Resistance

- Sulfonamide resistance may occur as a result of mutations that
  - cause **overproduction of PABA**,
  - cause production of a **folic acid-synthesizing enzyme** that has low affinity for sulfonamides, or
  - **impair permeability to the sulfonamide**

Sulphonamide analogues with reduced toxicity

The primary amino group of sulphonamides is acetylated in the body and the resulting amides have reduced solubility which can lead to toxic effects. For example, the metabolite formed from sulphathiazole (an early sulphonamide) is poorly soluble and can prove fatal if it blocks the kidney tubules .

It was discovered that the solubility problem could be overcome by replacing the thiazole ring in sulphathiazole with a pyrimidine ring to give sulphadiazine.

The reason for the improved solubility lies in the acidity of the sulphonamide NH proton. .

In sulphathiazole, this proton is not very acidic (high p K a). Therefore, sulphathiazole and its metabolite are mostly un-ionized at blood pH.

Replacing the thiazole ring with a more electron-withdrawing pyrimidine ring increases the acidity of the NH proton by stabilizing the resulting anion. Therefore, sulphadiazine and its metabolite are significantly ionized at blood pH.

As a consequence, they are more soluble and less toxic. Sulphadiazine was also found to be more active than sulphathiazole and soon replaced it in therapy. Silver sulphadiazine cream is still used topically to prevent infection of burns, although it is really the silver ions which provide the antibacterial effect

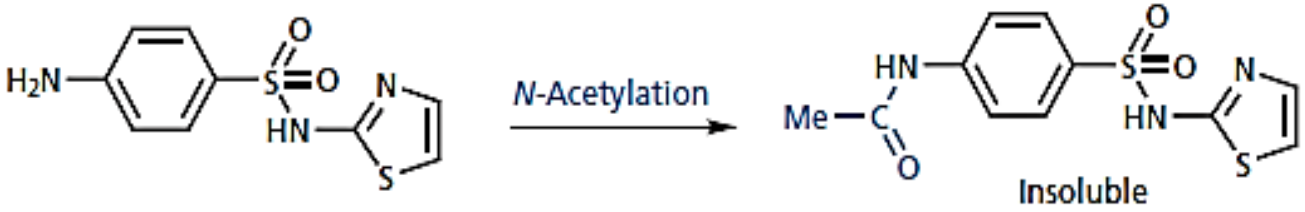


FIGURE 1 Metabolism of sulphathiazole.

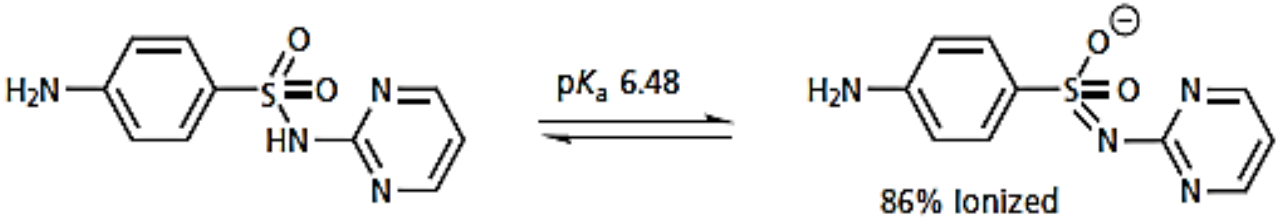


FIGURE 2 Sulphadiazine.

Applications of sulphonamides

The sulpha drugs presently have the following applications in medicine:

- treatment of urinary tract infections;
- eye lotions;
- treatment of infections of mucous membranes;
- treatment of gut infections .

It is also worth noting that sulphonamides have occasionally found uses in other areas of medicine

Treatment of intestinal infections

Sulphonamides have been particularly useful against intestinal infections, and can be targeted against these by the use of prodrugs. For example, succinyl sulphathiazole is a prodrug of sulphathiazole . The succinyl moiety contains an acidic group which means that the prodrug is ionized in the intestine. As a result, it is not absorbed into the bloodstream and is retained in the intestine. Slow enzymatic hydrolysis of the succinyl group then releases the active sulphathiazole where it is needed.

Benzoyl substitution on the aniline nitrogen has also given useful prodrugs that are poorly absorbed through the gut wall because they are too hydrophobic .

They can be used in the same way.

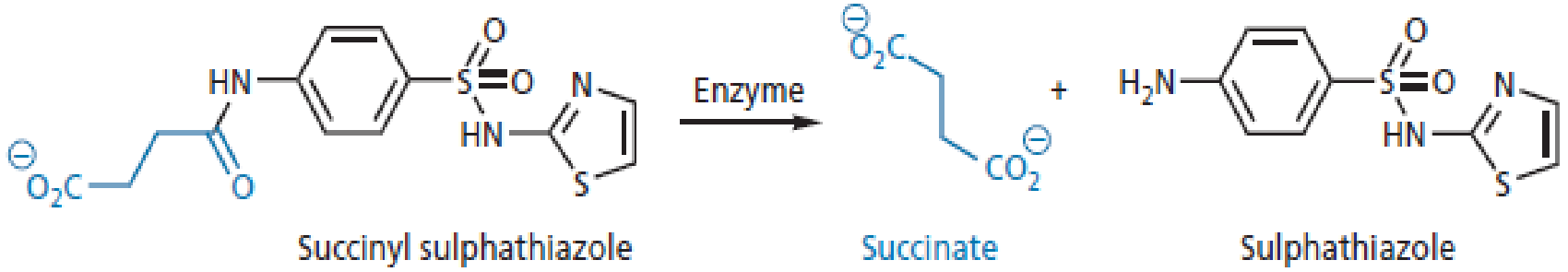


FIGURE 1 Succinyl sulphathiazole is a prodrug of sulphathiazole.

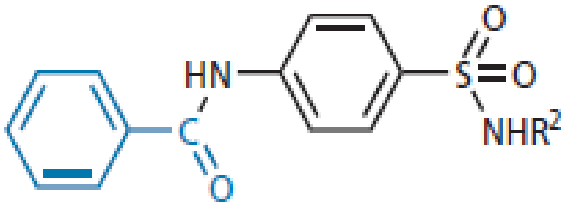


FIGURE 2 Substitution on the aniline nitrogen with benzoyl groups.

Trimethoprim

Trimethoprim is an orally active diaminopyrimidine structure, which has proved to be a highly selective antibacterial and antimalarial agent.

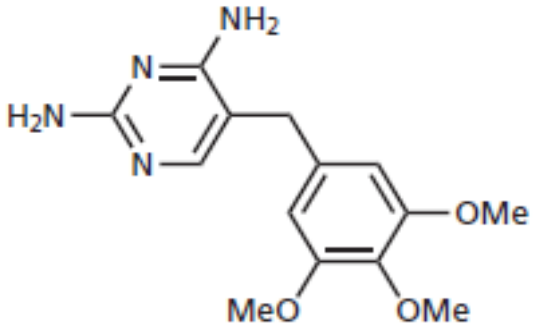
It acts against dihydrofolate reductase —the enzyme which carries out the conversion of dihydrofolate to tetrahydrofolate—leading to the inhibition of DNA synthesis and cell growth.

Trimethoprim is often given in conjunction with the sulphonamide sulphamethoxazole in a preparation called cotrimoxazole . It consists of one part trimethoprim to five parts sulfamethoxazole.

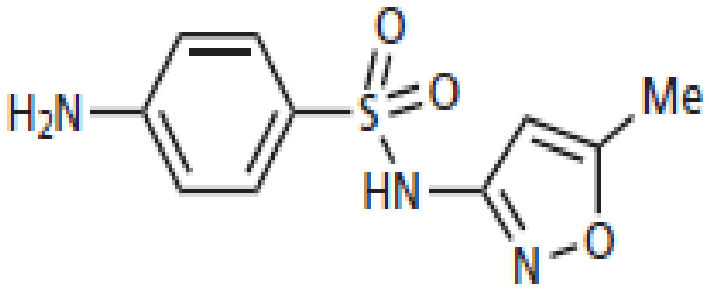
The sulphonamide inhibits the incorporation of PABA into dihydropteroate, while trimethoprim inhibits dihydrofolate reductase.

Therefore, two enzymes in the one biosynthetic route are inhibited .This is a very effective method of inhibiting a biosynthetic route and has the advantage that the doses of both drugs can be kept down to a safe level.

To get the same level of inhibition using a single drug, the dose level would have to be much higher, leading to possible side effects. This approach has been described as sequential blocking .



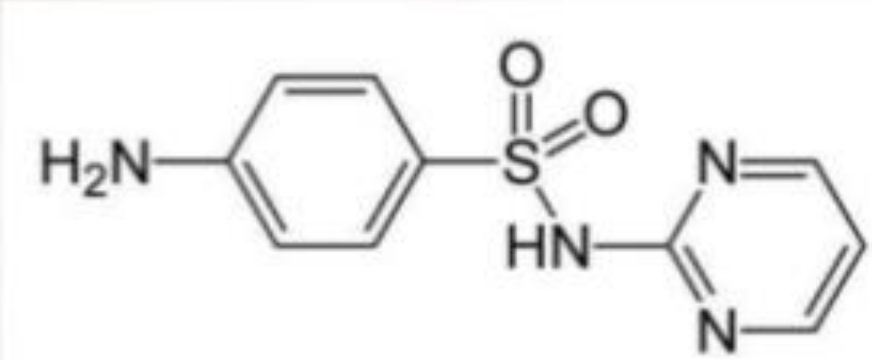
Trimethoprim (antimalarial)



Sulphamethoxazole

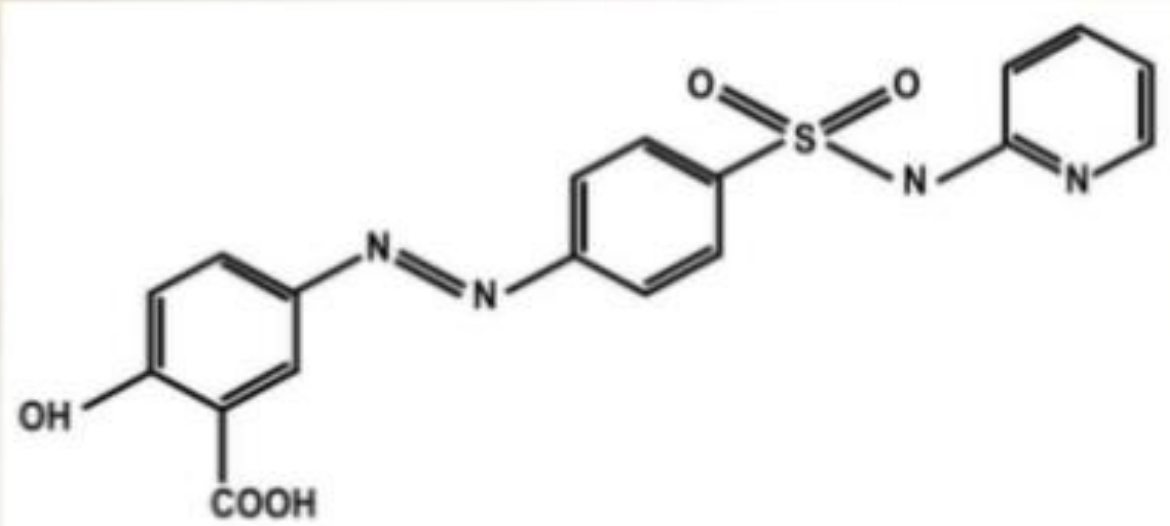
Clinical Use : **Topical Agents**

- **Sodium sulfacetamide ophthalmic solution** or ointment
  - effective in the treatment of bacterial conjunctivitis and as adjunctive therapy for trachoma.
- **Silver sulfadiazine**
  - infection of burn wounds



Clinical Use : **Oral Nonabsorbable Agents**

- Sulfasalazine (salicylazosulfapyridine)
  - Ulcerative colitis,
  - enteritis,
  - other inflammatory bowel disease



Sulfasalazine

Clinical Use : **Oral Absorbable Agents**

- **Sulfisoxazole and sulfamethoxazole**
  - urinary tract infections : adult dosage is 1 g of sulfisoxazole four times daily or 1 g of sulfamethoxazole two or three times daily
- **Sulfadiazine** in combination with **pyrimethamine** is first-line therapy for treatment of **acute toxoplasmosis**.
  - 1 g four times daily, with pyrimethamine given as a 75-mg loading dose followed by a 25-mg once-daily dose.
  - **Folinic acid**, 10 mg orally each day, should also be administered to minimize bone marrow suppression

Clinical Use : **Oral Absorbable Agents**

- **Sulfadoxine**
  - long-acting sulfonamide
  - combination formulation with pyrimethamine
  - a second-line agent in the treatment of malaria